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EXAMINER	
FOSTER, CHRISTINE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,797	SUNDREHAGEN, ERLING	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/14/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19,26 and 27* is/are rejected.

7)☒ Claim(s) *14-19,25 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/20/05, 9/20/06, 10/24/06, 2/6/07.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 14-19 and 26-27 in the reply filed on 7/14/08 is acknowledged. The traversal relates to the restriction requirement between Groups III and IV only and is on the ground(s) that the claims of Group IV have been currently amended so that Groups III-IV are now linked by the special technical combination of the specific-sized nanoparticles binder, in combination with turbidimetry (Reply, page 5). This is not found persuasive because although unity of invention has been reevaluated in light of the amended claims, the technical feature of calprotectin antibody-coated nanoparticles is not found to represent a contribution over the prior art for reasons detailed under § 103 below. Accordingly, the claims are not linked by a special technical feature such that unity of invention is lacking.

Applicant further argues that no undue search burden would be associated with searching Groups II and IV together (Reply, page 5, last paragraph). This is not found persuasive because Applicant is referring to the requirement to demonstrate search burden that pertains to applications filed under 35 U.S.C. 111(a) (see MPEP 801). There is no corresponding requirement to demonstrate search burden in applications filed under 35 U.S.C. 371.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-13 and 25 were canceled by Applicant. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/14/08 as discussed above.

3. Accordingly, claims 14-19 and 26-27 are subject to examination below.

Priority

4. The present application was filed on 12/19/2005 as a proper National Stage (371) entry of PCT Application No. PCT/GB03/05607, filed on 12/23/2003. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 0229747.1, filed on 12/20/2002 in the United Kingdom.

Information Disclosure Statement

5. The information disclosure statement filed **10/24/2006** fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Specifically, the non-patent literature publication by **Minno et al.** has not been considered because it is not in English and no explanation of relevance has been provided.

1. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Specifically, the title should refer to the determination of calprotectin. In addition, the words "cardiovascular disease" should be spelled out instead of using the abbreviation CVD.

3. The specification is objected to because required subject headings, e.g. the "BACKGROUND OF THE INVENTION," "BRIEF SUMMARY OF THE INVENTION," and the "BRIEF DESCRIPTION OF THE DRAWINGS" are absent. See MPEP § 608.01(a).

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.

(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

4. Claims 14-19 and 25-26 are objected to because of the following informalities:

5. Claim 14 refers to "a nanoparticle-bound anti-calprotectin antibody or antibody fragment" in the singular in part (b), while part (c) of the claim recites "the antibody or antibody fragment coated nanoparticles" in the plural. Clarification is needed as to whether there is one nanoparticles or a plurality.

6. Dependent claims 15-19 and 25-26 refer to preceding claims using the language a "method as claimed in claim [X]", which is ambiguous and may cause confusion. The language "The method of claim [X]" is suggested.

7. Regarding claims 26-27, it is suggested that in the first instance of the abbreviations "CNS" and "CVD" that these abbreviations be accompanied by their full terms.

8. Claim 16 is objected to regarding the parenthetical term "(e.g. monodisperse)", which may cause confusion as to whether the particles need be monodisperse or not.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 26-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention relates to a method for measuring calprotectin[1] by immunoturbidimetric assay. The claims at issue recite a method "for diagnosis of a disease" based on a comparison of calprotectin levels with a predetermined threshold value. The claims encompass diagnosis of a large number of disease conditions, including conditions that vary widely with respect to physiology, affected organ(s), symptomology, and etiology.

The specification reports the results of a study involving asymptomatic subjects who underwent EBCT testing, which measures coronary artery calcification (see specification, page 36). Calprotectin levels were measured in these subjects, and statistical analysis was performed in order to determine whether the levels were correlated with the extent of coronary artery calcification (as indicated by EBCT-generated calcium score or "CS"). See Example 6 and the Figures.

In particular, Figure 5 compares calprotectin levels in subjects who were calcium positive ("Cases", i.e., those who were observed to have coronary artery calcification) with levels in subjects who were calcium negative ("Controls"). See accompanying description on page 45, lines 5-7. Mean calprotectin levels in the calcium-negative subjects were 0.310 mg/L, while levels in the calcium-negative (disease) subjects were 0.375 mg/L (see page 45, lines 9-14). In

other words, mean levels of calprotectin were elevated by 0.065 mg/L in subjects who had coronary artery calcification. However, as reported in Table 1 (page 39), the standard deviations for the assays were well above this observed difference. See the row entitled "SD". In other words, calprotectin levels in different patients did not cluster closely together around the mean values of 0.310 and 0.375 mg/L, but rather were observed deviate far from these levels.

The prior art recognized that to be useful for diagnosis, biomarkers must possess certain characteristics. LaBaer et al. (*Journal of Proteome Research* (2005), Vol. 4, pages 1053-1059) teach that in general, much higher demands are placed on biomarkers to be used for diagnosis, and that quantitative values must be established in order to set the boundary between a positive and a negative test (see the paragraph bridging the left and right columns of page 1054). LaBaer et al. further teach that as a result, this requires that the measurements for individuals without the disease exhibit *relatively little variation*, since otherwise, establishing a cutoff value will be difficult (ibid). This scenario is depicted in Figure 5 of LaBaer et al. (see also p. 1056-1057), where it can be seen that if the mean values for healthy and disease populations overlap, it is difficult to establish a cutoff value that would separate the two populations.

In the instant case, the specification does not enable one to predictably employ calprotectin levels in diagnosis since the data reported do not support establishment of a quantitative value that would define the boundary between a positive and a negative test, which is recognized in the art to be a requirement for a diagnostic marker. Rather, the data reported indicate variation among individuals with and without disease (as indicated by the standard deviations reported for the assay).

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[1] Calprotectin is also referred to in the art as L1 protein, MRP 8/14, S100A8/A9, cystic fibrosis (associated) antigen,

Given the relatively small mean difference in calprotectin levels, and the fact that levels varied significantly in both disease and normal subjects, it is not apparent how the claimed assay methods could be used to diagnose disease based on calprotectin levels alone. The data reported do not support a statistically significant difference in calprotectin levels in the disease state, as evidenced by the largely overlapping levels in cases vs. controls. Consequently, one skilled in the art would face an undue burden of using calprotectin levels to diagnose cardiovascular disease as claimed, given that the same values of calprotectin are associated with both normal and disease states.

See also Hageman et al. (US 7,011,952 B2), which teaches that "significant" differences between healthy and control subjects can be used to signal a positive or negative outcome of a diagnostic test (column 8, line 61 to column 9, line 22). The reference teaches that the skilled artisan would considered differences to be "significant" if the measured value falls outside the range typically observed in normal subjects; for example "a departure can be considered significant if a measured level does not fall within the mean plus one standard deviation of levels in a control population" (see column 9, lines 7-13). The data presented in the specification would not be considered significant according to these guidelines.

Regarding the breadth of the claims, which encompass diagnosis of a large number of disease conditions—HIV infection, cancer, lung disease, and any type of cardiovascular disease, it is noted that such conditions vary widely with respect to physiology, affected organ(s), symptomology, and etiology.

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and other names as disclosed in the instant specification on page 3.

Despite such breadth, the data presented in the specification only examined calprotectin as a marker in the context of *coronary artery calcification* (a type of cardiovascular disease). Such teachings do not bear a reasonable correlation with the scope of the claims. Considering just "cardiovascular disease" out of the many diseases claimed, the breadth of the claims is apparent. Cardiovascular disease encompasses atrial fibrillation, heart valve disorders, high or low blood pressure, cardiomyopathy, deep vein thrombosis, varicose veins, and many others (see The Merck Manuals Online Medical Library, table of contents for the section "Heart and Blood Vessel Disorders", retrieved from http://www.merck.com/mmhe/sec03.html on 10/16/08; and also the instant specification at page 2, penultimate paragraph). The specification lacks guidance with regard to how to use calprotectin levels to diagnose these various disease conditions.

The specification also lacks any working examples in which calprotectin levels were used to diagnose *any* disease. In the clinical experiments discussed above, the presence of coronary artery calcification was determined by EBCT. Thus, the patients were those whose disease status was already known, and no working examples are reported in which diagnosis of disease was made based on calprotectin levels in subjects whose disease status was previously unknown.

More generally, one skilled in the art would recognize that in order to be employed in diagnosis, a biomarker must be specific to the disease to be diagnosed. See for example Mayeux et al. ("Biomarkers: Potential uses and Limitations"; NeuroRx (2004); Vol. 1, pages 182-188), which teaches that biomarkers are validated by a number of criteria, including the extent to which the biomarker correlates with the specific disease under study (page 186, left column, the first full paragraph).

In the instant case, Applicant apparently acknowledges that calprotectin is not specific to any one disease, as it is claimed that diagnosis of a large number of different diseases can be made based on calprotectin levels. Indeed, the prior art recognized calprotectin as a generalized inflammatory marker, one which is elevated in a variety of disease states. See for example Yui et al. ("Calprotectin (S100A8/S100A9), an Inflammatory Protein Complex from Neutrophils with a Broad Apoptosis-Inducing Activity"; Biol. Pharm. Bull. 26(6) 753-760 (2003)), which teaches that the prior high levels of calprotectin were reported in the prior art during various inflammatory conditions, such as rheumatoid arthritis, gingivitis, cystic fibrosis, abscesses, and others (the abstract; page 753, left column, last paragraph; and Table 1 in particular). Such teachings indicate that calprotectin was recognized in the prior art to be a generalized inflammatory marker that is elevated in various disease conditions.

Despite this lack of specificity to disease, the specification fails to provide direction or guidance with respect to *differential diagnosis*. Since calprotectin is elevated in a wide variety of diseases, it is not apparent how measurement of calprotectin levels alone could be used to diagnose any one out of the numerous possible claimed diseases. One of ordinary skill in the art would not know, upon observing altered levels of calprotectin in an asymptomatic subject (for example), whether to confer a diagnosis of HIV infection, cancer, cardiovascular disease (and *which* cardiovascular disease), etc. since the specification indicates that calprotectin levels would be altered in all of these diseases.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14-19 and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 14 recites that the diameter of the antibody or antibody fragment-coated nanoparticles is "**in the range 65-140 nm**". The use of the terminology "in the range" renders the indefinite because it is unclear whether Applicant intends to "in the range" to refer to the specific range of 65-140 nm, or alternatively whether the words "in the range" are meant as a qualifying statement indicating that the recited range is to be taken as approximate. In particular, the metes and bounds of the claims are unclear because it is not apparent whether only particles of diameter 65-140 nm would be included or also those having a diameter that approximates or is "in the range" of this range.

14. Claims 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which disease is diagnosed.

The preamble of claim 26 invokes a "method of diagnosis of a disease" but as written, the claim fails to recite any active method steps in which a disease is diagnosed. The claim includes a step in which calprotectin content is compared with a predetermined threshold value, but does not clearly relate this step back the objective of the method as stated in the preamble.

Either active method steps or alternatively, a correlation step describing how the results of the comparison step relate back to the objective of the method are suggested.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 14-19 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arvesen et al. ("Calprotectin: A Novel Plasma Marker of Granulocyte Activation in Acute Coronary Syndrome"; Circulation 1996; Vol 94(8), page 3015) in view of Craig et al. (US 4,480,042), or, in the alternative, as being unpatentable over Craig et al. in view of Arvesen et al.

Arvesen et al. teach that calprotectin is a marker of granulocyte activation in the context of acute coronary syndrome (title). Arvesen et al. studied patients with acute coronary syndrome (including unstable angina and non-Q myocardial infarction) and found that the patients had elevated levels of calprotectin in plasma as compared to healthy controls (see entire selection).

Arvesen et al. do not provide details regarding the assay method used to measure calprotectin, and therefore fail to specifically teach turbidimetric assessment using a nanoparticle of diameter 65-140 nm that is bound to a calprotectin antibody.

Craig et al. teach particle-based immunoassay methods, in which changes in turbidity caused by agglutination of particles can be used to measure unknown concentrations of compounds of biological interest (the abstract). The particles of Craig et al. have approximate diameter range of 0.03-0.1 μm (30-100 nm, i.e., "nanoparticles") and may have an antibody to the compound of interest covalently attached thereto (column 2, line 45 to column 5, line 32). For example, antibody particle reagents can be used in a direct particle enhanced turbidimetric immunoprecipitation assay, which provides increased detectability over conventional immunoprecipitation techniques, corresponding savings in reagent costs, and also allows for the use of smaller patient sample volumes (column 9, lines 23-33). Craig et al. also teach that turbidity measurements of immunological reactions using their particles are advantageous in that no special equipment is required other than a spectrophotometer (column 4, lines 59-63).

Therefore, it would have been obvious to one of ordinary skill in the art to determine the calprotectin in plasma as taught by Arvesen et al. using the particle-based turbidimetric immunoassay methods of Craig et al. In particular, it would have been obvious to coat the particles of Craig et al. with an antibody specific for calprotectin and to determine the calprotectin contect in the plasma samples by measuring changes in turbidity. The selection of a known method for its known purpose (detection of an unknown concentration of a substance of interest in a biological fluid sample) would have been obvious. In addition, one would have been motivated to employ the assay methods of Craig et al. because Craig et al. taught that such

methods do not require special equipment, provide increased detectability over conventional immunoprecipitation techniques, savings in reagent costs, and also allow for the use of smaller patient sample volumes, which would be particularly pertinent to the methods of Arvesen et al. in which calprotectin was measured in patient samples.

Regarding the limitation that the diameter of the antibody or antibody fragment-coated nanoparticles is in the range 65-140 nm, Craig et al. exemplifies particles having a diameter of 69 nm (Example 1, see especially at column 10, lines 57-58). However, Craig et al. do not indicate what size their particles would have after being coated with antibody.

However, the instant specification discusses on page 19 how the diameter of the particles may be measured either before or after the antibodies are bound to their surface: particle size ranges of 55-140, 65-110, and 70-90 nm are disclosed for "nude" particles, and size ranges of 65-140, 75-120, and 80-110 nm are disclosed for antibody-coated particles. Such teachings indicate that coating of an antibody would result in an approximate 10-nm increase in particle size diameter; i.e., from 69 to 79 nm in the case of the Craig et al. particles.

For these reasons, there is a strong scientific basis to believe that the particles of Craig et al., when coated with antibody, would have a diameter falling within the claimed ranges of 65-140 nm and 75-120 nm as recited in instant claims 14-15. Because the claimed and prior art products appear to be identical or substantially identical, Applicant has the burden of advancing evidence to show that they are not. See MPEP 2112.

Notwithstanding the above, the Examiner also notes that Craig et al. teach that it is important to select the particle size with care in order to optimize the turbidity change which occurs during agglutination (column 5, lines 1-2). Given this recognition of particle size as a

result-effective variable, it would also have been obvious to arrive at the claimed size ranges out of the course of routine optimization, given the normal desire of artisans to improve upon what is already known. See MPEP 2144.05.

One would have a reasonable expectation of success because Craig et al. taught that their particle-based immunoassay methods can be used for detecting a wide variety of substances in biological fluids (including plasma). See column 9, lines 8-22.

It is also possible to analyze the teachings of Craig et al. in view of those of Arvesen et al. Craig et al. teach an assay method for the determination of compounds of interest in biological samples, comprising the steps of obtaining a biological fluid sample, contacting the sample with a nanoparticle-bound antibody specific for the compound of interest; and assessing the concentration of the compound of interest by turbidimetry. See passages noted above and claim 1 in particular.

The Craig et al. reference differs from the claimed invention, however, in that the reference fails to teach determination of the analyte calprotectin.

However, in light of the teachings of Arvesen et al. that calprotectin is a marker of granulocyte activation in acute coronary syndrome, it would have been obvious to one of ordinary skill in the art to employ the assay method of Craig et al. to determine calprotectin as an analyte of clinical interest. In particular, it would have been obvious to coat the particles of Craig et al. with an anti-calprotectin antibody and to determine the calprotectin concentration in plasma samples.

With respect to claim 16, Craig et al. teach that the final particle size is controllable and is substantially uniform (column 5, lines 20-25).

With respect to claim 17, Craig et al. teach that the agglutination reaction can be accelerated by the presence of an agglutinating enhancer (i.e., an opacity enhancer) such as polyethcylene glycol or sodium dodecyl sulfate (column 10, lines 16-22 and claims 2-3). Although Craig et al. do not specifically teach when the enhancer is added, the selection of any order of mixing ingredients would have been prima facie obvious. See MPEP 2144.04(C).

With respect to claim 19, Craig et al. exemplify use of a clinical analyzer instrument in performing their assay methods (Example 5, see especially column 12, lines 39-56). It would have been further obvious when performing the particle-based turbidimetry immunoassay for calprotectin of Craig et al. and Arvesen et al. to similarly employ a clinical analyzer, which would be considered to be an "automated" assay absent a specific or limiting definition in the instant specification.

In addition, the courts have ruled that broadly providing an automatic or mechanical means to replace a manual activity which accomplishes the same result is not sufficient to distinguish over the prior art. See MPEP 2144.04(III). Therefore, when taken together with the general knowledge in the art, it would also have been obvious to automate the assay method of Craig et al. and Arvesen et al.

With respect to claims 26-27, Arvesen et al. compared plasma calprotectin levels with mean levels in healthy control subjects (see the table under "Results"). Such a mean value would be considered a "predetermined threshold value" when this terminology is given its broadest reasonable interpretation, in that normal levels of calprotectin may be said to be physiologically predetermined.

The Examiner also notes as discussed above under 112, 2nd paragraph that while the preamble of claims 26-27 refer to "diagnosis of a disease" (which may be CVD), the claims do not include any actual steps in which disease is diagnosed. Such statements in the preamble therefore do not provide antecedent basis for terms in the body of the claim and are not essential to understand the limitations or terms in the claim body. In addition, the preamble normally recites the purpose or intended use of the claimed invention. Such statements merely define the

context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3).

When the claims are given their broadest reasonable interpretation, therefore, the reference to diagnosis of CVD may be interpreted as simply a statement of a possible application or intended use of the claimed methods. Absent any limitations that would distinguish the patient population upon whom the method is performed (for example), the reference to diagnosis of disease in the preambles is not sufficient to distinguish over the art. In teaching the recited comparison step, the teachings of Arvesen et al. (when taken together with those of Craig et al.) read on the claim.

Even if the references to "diagnosis of a disease" are given weight in the claims, the invention is nonetheless found obvious for the following reasons. Arvesen et al. clearly teach calprotectin as a marker in the context of acute coronary syndrome (i.e., cardiovascular disease), documenting elevated calprotectin levels in patients with this disorder.

It is asserted that it was well known in the art at the time of the invention that disease processes may produce changes in the levels of certain analytes, and that measurement of the levels of such analytes could be used to detect the presence of the disease. It is also asserted that it was well know in the art to compare marker values to threshold or cut-off levels associated with either of normal or disease state marker levels.

Consequently, although Arvesen et al. measured calprotectin levels in subjects whose disease status was already known (i.e., subjects already diagnosed with disease), based on their findings that calprotectin levels are elevated in acute coronary syndrome so as to qualify as a "marker", one of ordinary skill in the art would have found it obvious to detect calprotectin as a

biomarker for the purpose of diagnosing acute coronary syndrome in unknown subjects. When taken together with the general knowledge in the art, it would have been further obvious to compare a patient's measured calprotectin levels to threshold levels in accordance with routine procedures in the art of clinical diagnostics.

Conclusion

It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 103(a). While these rejections may seem contradictory, they are not, because each is based upon a different legal analysis, i.e., sufficiency of the disclosure of the instant application to support claims under 35 USC, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783(CCPA 1969)).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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